INHALABLE LEVODOPA: FROM LABORATORY TO THE PATIENT

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Colophon

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CONTENTS

Chapter 1	Inhaled drugs for systemic action	11
Chapter 2	Can patients with Parkinson's disease use dry powder inhalers during off periods? PLoS One. 2015 Jul 14;10(7):e0132714	29
Chapter 3	A levodopa dry powder inhaler for the treatment of parkinson's disease patients in off periods. Eur J Pharm Biopharm. 2015 Nov, 97(PT A):22-9.	45
Chapter 4	Pharmacokinetics and tolerability of inhaled levodopa from a new dry powder inhaler in Parkinson's disease patients. Ther Adv Chronic Dis 2019, Vol. 10: 1-10.	63
Chapter 5	Learning from Parkinson's patients: usability of the cyclops dry powder inhaler. Int J Pharm. Volume 567, August 2019.	79
Chapter 6	Effectiveness of inhaled levodopa in Parkinson's disease. A summary of the study design (NTR7054).	93
Chapter 7	General discussion and practical implications for future use.	105
Appendix A	Summary	115
Appendix B	Samenvatting	123
	Curriculum Vitae	130
	List of Publications	131
	Dankwoord	133

PROLOGUE

There is a growing interest in using the pulmonary route for the administration of systemically acting drugs. This route of administration may have certain specific advantages. It may, for example, overcome problems with drugs that have a low or variable bioavailability when given via other routes of administration such as the oral route. Pulmonary administration may also be of advantage with drugs that, due to pylorospasm or gastroparesis, have problems passing from the stomach to the small intestine where the absorption has to take place, as is the case for levodopa in Parkinson's disease (1). Parkinson's disease is a progressive degenerative disorder and many patients suffer from off periods at some stage of their disease. During off periods, motor symptoms of the disease are poorly controlled and a rapid onset of effect of the anti-Parkinson drug is wanted. Since levodopa is a small molecule (±197 Da) that can rapidly pass the pulmonary membranes it is an interesting candidate for pulmonary delivery, in case an immediate action of the drug is desired. Moreover, the gastro-intestinal and first-pass metabolism can be circumvented by using the pulmonary route.

However, systemic drug delivery using inhaled aerosols is accompanied by several specific requirements and challenges. Small molecules like levodopa can be absorbed over both the airway and alveolar membranes (2). The major determinant for a successful administration is the lung-dose that can be achieved with inhalation. Whether pulmonary administration is possible and to which extent it will be successful depends on many factors, including the tolerability of the drug, the drug formulation and the inhaler technology as well as on how the inhalers are used by the patients. And even after successful delivery to the lungs, the destiny of the particles after deposition at the site of absorption is often still uncertain. Metabolism and clearance mechanisms in the lungs may be effective in degradation and removal respectively, thereby diminishing the bioavailability of the drug (3). This all makes the entire process from drug aerosolization to systemic therapeutic effect very complex and challenging.

This thesis starts with a detailed review about the requirements and uncertainties regarding the pulmonary delivery of systemically acting drugs in general. Since we are interested in the systemic delivery of levodopa by inhalation, the next chapter discusses the applicability of a levodopa dry powder inhaler during off periods in Parkinson's disease patients. For effective delivery in the peripheral airways, it is a prerequisite that Parkinson's patients are able to perform an adequate inhalation manoeuvre. However, such a manoeuvre consists of different steps that have to be performed in the right order. It can be imagined that this may be hard for a Parkinson's patient, especially in an off period, when the motor function is disturbed and symptoms of the disease are poorly controlled. An easy to perform preparation and inhalation procedure are therefore of paramount importance to achieve successful drug administration. In this thesis chapter 2 investigates whether or not patients with Parkinson's disease are able to perform an adequate inhalation procedure with the inhaler we developed. As described in chapter 5, the ability of

Parkinson's patients to prepare the Cyclops inhaler for use was studied, since the disturbed motor function of Parkinson's disease patients may be of influence. A next step in the development of a good inhalation product would be the development of a suitable powder formulation. In chapter 3, we describe the development of a levodopa formulation that contains only 2% excipient, which is quite unique.

Next, the results of a pharmacokinetic and tolerability study in Parkinson's patients with the developed inhalation powder and inhaler combination are described in chapter 4. Finally the study protocol of a trial regarding the effect of levodopa inhalation powder on the recovery of off periods is shown. The study is currently ongoing and if the results are positive, this opens the way to further development and upscaling of our levodopa inhalation powder for use in the recovery from off periods.

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